



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(54) Title: <b>INTERLEUKIN-1 INHIBITOR</b>			
<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;"> <p>(I)</p> </div> <div style="text-align: center;"> <p>(II)</p> </div> </div>			
(57) Abstract			
<p>An interleukin-1 inhibiting agent which comprises as an active ingredient a benzoheterocyclic compound of formula (I) or (II) wherein R<sup>1</sup> and R<sup>2</sup> are each a lower alkyl group and X<sup>1</sup> is a halogen atom, R<sup>3</sup> is a lower alkyl group, R<sup>4</sup> is a hydroxy group, and X<sup>2</sup> is a halogen atom, or a pharmaceutically acceptable salt, and a method for prophylaxis and treatment of various diseases induced by acceleration of IL-1 secretion by administering said interleukin-1 inhibiting agent.</p>			

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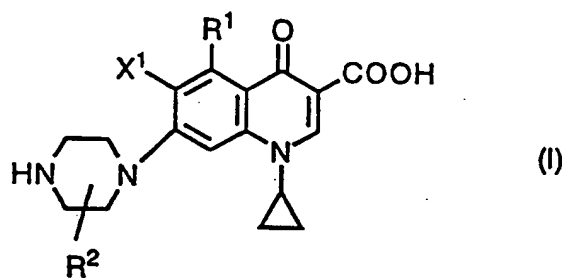
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## DESCRIPTION

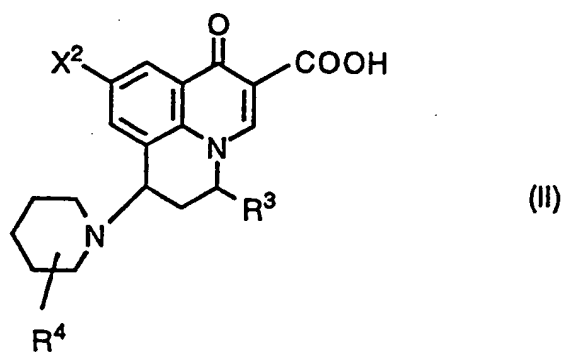
## INTERLEUKIN-1 INHIBITOR

## TECHNICAL FIELD

This invention relates to an interleukin-1 inhibitor, more particularly to an interleukin-1 inhibiting agent comprising as an active ingredient at least one of benzoheterocyclic compounds selected from the group consisting of 1,4-dihydro-4-oxoquinoline-3-carboxylic acids of the formula:



wherein R<sup>1</sup> and R<sup>2</sup> are each a lower alkyl group and X<sup>1</sup> is a halogen atom, or a salt thereof, and 6,7-dihydro-1-oxo-1H,5H-benzo[i,j]quinolidine-2-carboxylic acids of the formula:



wherein R<sup>3</sup> is a lower alkyl group, R<sup>4</sup> is hydroxy group, and X<sup>2</sup> is a halogen atom, or a salt thereof.

## BACKGROUND ART

It has been decided in the 2nd International Lymphokine Workshop

that the physiologically active substance, which had been called by various names such as Lymphocyte Activating Factor (LAF), Mitogenic Protein, Helper peak-1, T-cell replacing factor III (TRF-III), T-cell replacing factor macrophage (TRFM), B-cell activating factor, B-cell differentiation factor, has uniformly been designated as "interleukin-1" (IL-1) [cf. Cellular Immunol., 48, 433-436 (1979)]. This is decided by the reason that the above physiologically active substance having various namings could not be distinguished from each other and had been designated merely based on different angles of the physiological activities.

It has been known that the above IL-1 is a biomaterial which is important for inducing and transmitting the systemic biological response against infection and inflammation, and further this substance per se has a strong antitumor activity [cf. Hirai, Y., et al.; "Gann Monograph on Cancer Research", Japan Scientific Societies Press, Tokyo (1988)], and further it has also been found that it induces response observed in the inflammation in vivo, such as fever, increase of leukocytes, activation of lymphocytes, induction of biosynthesis of acute phase protein in liver [cf. Dinarello, C.A.; Interleukin-1, Rev. Infect. Des., 6, 51-95 (1984), and Kluger, M.J., Oppenheim, J.J. & Powanda, M.C.; The Physiologic, Metabolic and Immunologic Actions of Interleukin-1, Alan R. Liss, Inc., New York (1985)].

Moreover, IL-1 has various biological activities and has been considered to be an important factor for maintaining the homeostasis, but when the function of IL-1 production is disordered and thereby IL-1 is produced in an abnormally larger amount, it may cause various diseases. For example, it has been reported that in case of rheumatoid arthritis, there is a strong correlation between the degree of inflammation of articular synovium and the degree of the

bone destruction and expression of HLA-DR antigen in the synovial tissue [cf. Miyasaka, N., Sato, K., Goto, M., Sasano, M., Natsuyama, M., Inoue, K., and Nishioka, K.; Augmented Interleukin-1 Production and HLA-DR Expression in the Synovium of Rheumatoid Arthritis Patient: *Arthritis Rheum.*, 32, (4), 476-480 (1988)].

Accordingly, it is considered that the various physiological properties associated with IL-1 may be blocked by inhibiting the excess release of IL-1 from cells.

There are used glucocorticoid hormones for the treatment of chronic inflammatory diseases, and it is known that the activities will partly be due to the suppression of IL-1 production [cf. Lew, W., Oppenheim, J.J., & Matsushima, K.; Analysis of the Suppression of IL-1 $\alpha$  and IL-1 $\beta$  Production in Human Peripheral Blood Mononuclear Adherent Cells by a Glucocorticoid Hormone: *J. Immunol.*, 140, (6), 1895-1902 (1988)]. However, it has been known that glucocorticoids induce disadvantageously various heavy side effects owing to its various physiological activities.

Thus, it has been desired to find a new drug which has no side effects as observed in glucocorticoids and further has excellent safety in the toxicity and other side effects for the purpose of the treatment of chronic inflammatory diseases such as rheumatoid arthritis, psoriasis, autoimmune diseases.

By the way, the 1,4-dihydro-4-oxoquinoline-3-carboxylic acids of the formula (I) and the 6,7-dihydro-1-oxo-1H,5H-benzo[i,j]quinolidine-2 - carboxylic acids of the formula (II) are disclosed in European Patent Publication

0287951 and U.S. Patent 4,399,134 as antibacterial agents.

#### DISCLOSURE OF THE INVENTION

The present inventors have studied to develop a new interleukin-1 inhibitor and have found that the benzoheterocyclic compounds of the formulae (I) and (II), particularly 7-(3-methyl-1-piperazinyl)-1-cyclopropyl-6-fluoro-5-methyl -  
5 1,4-dihydro-4-oxoquinoline-3-carboxylic acid or a salt thereof and 9-fluoro-8-(4 - hydroxy-1-piperidiny)-5-methyl-6,7-dihydro-1-oxo-1H,5H-benzo[ji]quinolidine-2 - carboxylic acid or a salt thereof are useful as an interleukin-1 inhibitor.

An object of the invention is to provide a novel interleukin-1  
10 inhibiting agent. Another object of the invention is to provide a new use of the known benzoheterocyclic compounds of the formulae (I) and (II) and their salts as an interleukin-1 inhibitor. A further object is to provide a method for the prophylaxis and treatment of various diseases induced by acceleration of interleukin-1 secretion by administering an effective amount of the  
15 benzoheterocyclic compounds (I) or (II) or a salt thereof to the subject suffering from such diseases.

The each group in the formulae (I) and (II) denotes as follows.

The "lower alkyl group" denotes a straight chain or branched chain alkyl group having 1 to 6 carbon atoms, such as methyl, ethyl, propyl, isopropyl,  
20 butyl, tert-butyl, pentyl, hexyl, and the like.

The "halogen atom" denotes fluorine, chlorine, bromine or iodine atom.

Among the benzoheterocyclic compounds of the formulae (I) and (II), basic compounds can easily form a salt with conventional pharmaceutically  
25 acceptable acids. These acids include, for example, inorganic acids such as

sulfuric acid, nitric acid, hydrochloric acid, phosphoric acid, hydrobromic acid, etc., and organic acids such as acetic acid, p-toluenesulfonic acid, ethanesulfonic acid, oxalic acid, maleic acid, fumaric acid, malic acid, tartaric acid, citric acid, succinic acid, benzoic acid, etc. Besides, among the

5 benzoheterocyclic compounds of the formulae (I) and (II), acidic compounds can easily form a salt with conventional pharmaceutically acceptable basic compounds. These basic compounds include, for example, sodium hydroxide, potassium hydroxide, calcium hydroxide, sodium carbonate, potassium hydrogen carbonate, etc.

10 The interleukin-1 inhibitor of the present invention is useful for the prophylaxis and treatment of various diseases induced by acceleration of interleukin-1 secretion, for example, autoimmune diseases such as nephritis, vasculitis, and inflammatory bowel disease (e.g. ulcerative colitis or Crohn's disease); rheumatic diseases such as rheumatoid arthritis, psoriatic arthritis, 15 scleroderma, Behçet's disease, and gout; inflammatory diseases associated with local and systemic infection such as septic shock and inflammatory diseases in dental, ophthalmic and otorhinologic fields such as chronic periodontal disease, ocular inflammatory disease, and otitis media; allergic diseases such as asthma; osteoporosis; endometriosis [cf. Fukih, H. et al; Fertil. Steril., 47, p213 (1987)]; 20 chronic granulomatous disease; Hodgkin's disease; acute or chronic myelogenous leukemia; graft-vs.-host disease; diabetes [cf. Dayer Metroz M.-D.; Eur. J. Clin. Invest., 22 (No. 4), p2, A50 (1992)]; Kawasaki's disease [cf. Leung, D.Y.M. et al; J. Exp. Med., 164, p1958 (1986)]; and the like.

25 The compounds of the formulae (I) and (II) and their salts of the present invention are used in the form of a conventional pharmaceutical preparation in

human being and other animals. The preparation is prepared by using conventional diluents or carriers such as fillers, thickening agents, binders, wetting agents, disintegrators, surfactants, lubricants, and the like. The pharmaceutical preparations may be selected from various forms in accordance with the desired utilities, and the representative forms are tablets, pills, powders, solutions, suspensions, emulsions, granules, capsules, suppositories, injections (solutions, suspensions, etc.), and the like. In order to form in tablets, there are used conventional carriers such as vehicles (e.g. lactose, white sugar, sodium chloride, glucose, urea, starches, calcium carbonate, kaolin, crystalline cellulose, silicic acid, etc.), binders (e.g. water, ethanol, propanol, simple syrup, glucose solution, starch solution, gelatin solution, carboxymethyl cellulose, shellac, methyl cellulose, potassium phosphate, polyvinylpyrrolidone, etc.), disintegrators (e.g. dry starch, sodium arginate, agar powder, laminaran powder, sodium hydrogen carbonate, calcium carbonate, polyoxyethylene sorbitan fatty acid esters, sodium laurylsulfate, stearic monoglyceride, starches, lactose, etc.), disintegration inhibitors (e.g. white sugar, stearin, cacao butter, hydrogenated oils, etc.), absorption promoters (e.g. quaternary ammonium base, sodium laurylsulfate, etc.), wetting agents (e.g. glycerin, starches, etc.), adsorbents (e.g. starches, lactose, kaolin, bentonite, colloidal silicates, etc.), lubricants (e.g. purified talc, stearates, boric acid powder, polyethylene glycol, etc.), and the like. Moreover, the tablets may also be in the form of a conventional coated tablet, such as sugar-coated tablets, gelatin-coated tablets, enteric coated tablets, film coating tablets, or double or multiple layer tablets.

In the preparation of pills, the carriers include vehicles (e.g. glucose, lactose, starches, cacao butter, hydrogenated vegetable oils, kaolin,

talc, etc.), binders (e.g. gum arabic powder, tragacanth powder, gelatin, ethanol, etc.), disintegrators (e.g. laminaran, agar, etc.), and the like. In the preparation of suppositories, the carriers include, for example, polyethylene glycol, cacao butter, higher alcohols, higher alcohol esters, gelatin, semi-synthetic glycerides, and the like.

Capsules can be prepared by charging a mixture of the compound of this invention with the above carriers into hard gelatin capsules or soft capsules in a usual manner.

In the preparation of injections, the solutions, emulsions or suspensions are sterilized and are preferably made isotonic with the blood. In the preparation of these solutions, emulsions and suspensions, there are used conventional diluents, such as water, macrogol, ethyl alcohol, propylene glycol, ethoxylated isostearyl alcohol, polyoxylated isostearyl alcohol, polyoxyethylene sorbitan fatty acid esters, and the like. In this case, the pharmaceutical preparations may also be incorporated with sodium chloride, glucose or glycerin in an amount sufficient to make them isotonic, and may also be incorporated with conventional solubilizers, buffers, anesthetizing agents.

Besides, the pharmaceutical preparations may optionally be incorporated with coloring agents, preservatives, perfumes, flavors, sweetening agents, and other medicaments, if desired.

The amount of the active compound to be incorporated into the interleukin-1 inhibiting agent of this invention is not specified but may be selected from a broad range, but it is usually in the range of 1 to 70% by weight, preferably about 1 to 30% by weight.

The interleukin-1 inhibiting preparation of this invention may be

administered in any method, and suitable method for administration may be determined in accordance with various forms of preparation, ages, sexes and other conditions of the patients, the degree of severity of diseases, and the like. For example, tablets, pills, solutions, suspensions, emulsion, granules and capsules are administered orally. The injections are intravenously administered alone or together with a conventional auxiliary liquid (e.g. glucose, amino acid solutions), and further are optionally administered alone in intramuscular, intracutaneous, subcutaneous, or intraperitoneal route, if desired. Suppositories are administered in intrarectal route.

The dosage of the interleukin-1 inhibiting agent of this invention may be selected in accordance with the usage, ages, sexes and other conditions of the patients, the degree of severity of the diseases, and the like, but is usually in the range of about 0.1 to 1000 mg of the active compound of this invention per 1 kg of body weight of the patient per day. The daily dosage may be administered dividedly in one to four times in a day. The active compound is preferably contained in an amount of about 1 to about 600 mg per the dosage unit.

#### BEST MODE FOR CARRYING OUT THE INVENTION

The present invention is illustrated by the following preparations and pharmacological experiments.

##### Preparation 1

Film coated tablets are prepared from the following components.

<u>Components</u>	<u>Amount</u>
7-(3-Methyl-1-piperazinyl)-1-cyclopropyl-6-fluoro-5-methyl-1,4-hydroxy-4-oxoquinoline-3-carboxylic acid	150 g

	Abicel (tradename of microcrystalline cellulose, manufactured by Asahi Chemical Industry Co., Ltd., Japan)	40 g
5	Corn starch	30 g
	Magnesium stearate	2 g
	Hydroxypropyl methylcellulose	10 g
	Polyethylene glycol-6000	3 g
	Castor oil	40 g
10	Ethanol	40 g

The active component of this invention, Avicel, corn starch and magnesium stearate are mixed and kneaded and the mixture is tabletted using a conventional pounder (R 10 mm) for sugar coating. The tablets thus obtained are coated with a film coating agent consisting of hydroxypropyl methylcellulose, polyethylene glycol-6000, castor oil and ethanol to give film coated tablets.

#### Preparation 2

Tablets are prepared from the following components.

	<u>Components</u>	<u>Amount</u>
20	9-Fluoro-8-(4-hydroxy-1-piperidiny)-5-methyl- 6,7-dihydro-1-oxo-1H,5H-benzof[ji]quinolidine- 2-carboxylic acid	150 g
	Citric acid	1.0 g
	Lactose	33.5 g
25	Dicalcium phosphate	70.0 g
	Pluronic F-68	30.0 g
	Sodium laurylsulfate	15.0 g
	Polyvinylpyrrolidone	15.0 g

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	Polyethylene glycol (Carbowax 1500)	4.5 g
	Polyethylene glycol (Carbowax 6000)	45.0 g
	Corn starch	30.0 g
	Dry sodium laurylsulfate	3.0 g
5	Dry magnesium stearate	3.0 g
	Ethanol	q.s.

The active compound of this invention, citric acid, lactose, dicalcium phosphate, Pluronic F-68 and sodium laurylsulfate are mixed. The mixture is screened with No. 60 screen and is granulated in wet with an alcohol solution containing polyvinylpyrrolidone, carbowax 1500 and 6000. If required, an alcohol is added thereto so that the powder mixture is made a paste-like mass. Corn starch is added to the mixture and the mixture is continuously mixed to form uniform particles. The resulting particles are passed through No. 10 screen and entered into a tray and then dried in an oven at 100°C for 12 to 14 hours. The dried particles are screened with No. 16 screen and thereto are added dry sodium laurylsulfate and dry magnesium stearate, and the mixture is tabletted to form the desired shape.

The core tablets thus prepared are vanished and dusted with talc in order to guard from wetting. Undercoating is applied to the core tablets. In order to administer the tablets orally, the core tablets are vanished several times. In order to give round shape and smooth surface to the tablets, further under-coating and coating with lubricant are applied thereto. The tablets are further coated with a coloring coating material until the desired colored tablets are obtained. After drying, the coated tablets are polished to obtain the desired tablets having uniform gloss.

Pharmacological experiment

Method: A 10% heparinized preperal blood from healthy volunteer, a test compound and lipopolysaccharide (LPS, 3.3  $\mu\text{g/ml}$ ) were suspended in RPMI-1640 medium supplemented with penicillin 100 units/ml and streptomycin 0.1  $\mu\text{g/ml}$ , and the mixture was incubated in a 5%  $\text{CO}_2$  atmosphere at 37°C for 18 - 24 hours. The supernatant of the culture was collected by centrifugation.

The IL-1 $\alpha$  and IL-1 $\beta$  isolated from cells by stimulation with LPS were measured by enzyme-linked immunoassay (ELISA). That is, 96-well ELISA plate was coated with a mouse monoclonal antibody against human IL - 1 $\alpha$  or human IL-1 $\beta$ , followed by blocking treatment, and thereto was added a test sample and it was subjected to reaction. After the reaction, the plate was washed, and then rabbit polyclonal antibody against IL-1 $\alpha$  or IL-1 $\beta$  was added to the plate and subjected to reaction. After washing the plate, horseradish peroxidase (POD)-conjugated anti-rabbit immunoglobulin was added thereto and subjected to reaction. After removing the unbound POD-conjugated antibody by washing, a substrate solution (containing ortho-phenylenediamine and hydrogen peroxide) was added and subjected to reaction, and thereafter, the absorbance at 492 nm was measured, and thereby the amounts of IL-1 $\alpha$  and IL-1 $\beta$  were measured based on each standard curve. The ratio (%) of inhibition of IL-1 release was calculated by the following equation:

$$\text{IL-1 release inhibitory ratio (\%)} = 100 \times (1 - T/C)$$

wherein T means the amount of IL-1 in the supernatant of culture incorporated

with the test compound, and C means the amount of IL-1 in the supernatant of culture added only with the solvent.

Test compounds:

1. 7-(3-Methyl-1-piperazinyl)-1-cyclopropyl-6-fluoro-5-methyl-  
1,4-dihydro-4-oxoquinoline-3-carboxylic acid.
2. 9-Fluoro-8-(4-hydroxy-1-piperidinyl)-5-methyl-6,7-di-  
hydro-1-oxo-1H,5H-benzo[ji]quinolidine-2-carboxylic acid.

Results:

The results are shown in Table 1.

Table 1

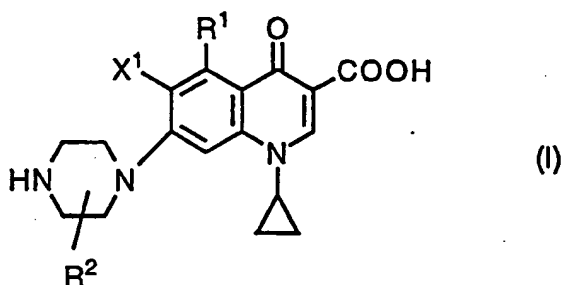
Test compounds	Dose ( $3 \times 10^{-5}$ g/ml)	
	IL-1 $\alpha$ release inhibitory ratio	IL-1 $\beta$ release inhibitory ratio
1	93 %	96 %
2	82 %	78 %

INDUSTRIAL APPLICATION

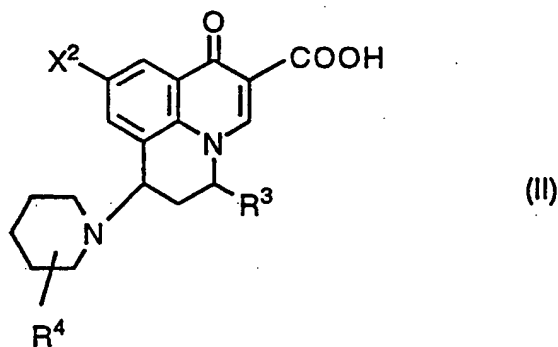
The interleukin-1 inhibiting agent of this invention is useful for the prophylaxis and treatment of various diseases induced by acceleration of IL-1 secretion, such as autoimmune diseases, rheumatic diseases, various inflammatory diseases, allergic diseases, and the like in human being and other animals.

## CLAIMS

1. An interleukin-1 inhibiting agent which comprises as an active ingredient a benzoheterocyclic compound of the formula:



wherein  $R^1$  and  $R^2$  are each a lower alkyl group and  $X^1$  is a halogen atom, or



25 wherein  $R^3$  is a lower alkyl group,  $R^4$  is hydroxy group, and  $X^2$  is a halogen atom, or a pharmaceutically acceptable salt thereof.

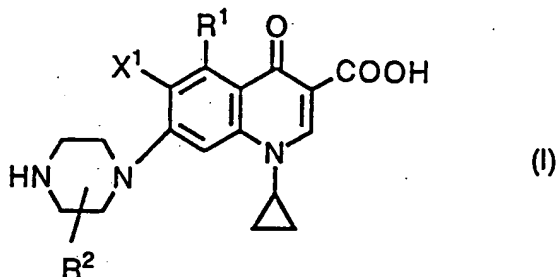
2. The agent according to claim 1, wherein the active compound is 7-(3-methyl-1-piperazinyl)-1-cyclopropyl-6-fluoro-5-methyl-1,4-dihydro-4-oxoquinoline-3-carboxylic acid or 9-fluoro-8-(4-hydroxy-1-piperidinyl)-5-methyl-6,7-dihydro-1-oxo-1H,5H-benzof[ji]quinolidine-2-carboxylic acid, or a pharmaceutically acceptable salt thereof.

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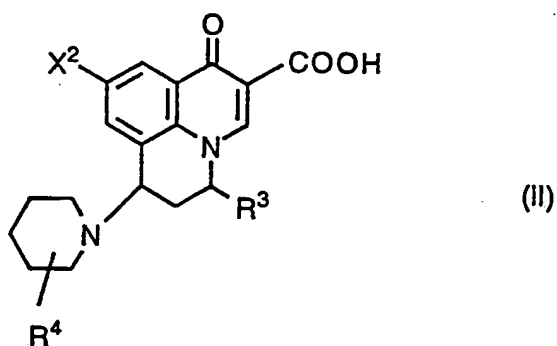
3. A method for the prophylaxis and treatment of diseases induced by acceleration of interleukin-1 secretion which comprises administering a therapeutically effective amount of a benzoheterocyclic compound of the

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formula:



wherein  $R^1$  and  $R^2$  are each a lower alkyl group and  $X^1$  is a halogen atom, or



wherein  $R^3$  is a lower alkyl group,  $R^4$  is hydroxy group, and  $X^2$  is a halogen atom, or a pharmaceutically acceptable salt thereof to a subject suffering from the diseases.

25

4. The method according to claim 3, wherein the diseases induced by acceleration of interleukin-1 secretion is autoimmune diseases, rheumatic diseases, inflammatory diseases associated with local and systemic infection, allergic diseases, osteoporosis, endometriosis, chronic granulomatous disease, Hodgkin's disease, acute or chronic myelogenous leukemia, graft-vs.-host disease, diabetes, and Kawasaki's disease.

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5. The method according to claim 4, wherein the diseases induced by acceleration of interleukin-1 secretion is autoimmune diseases and rheumatic diseases.

6. The method according to claim 3, 4 or 5, wherein the active compound is 7-(3-methyl-1-piperazinyl)-1-cyclopropyl-6-fluoro-5-methyl-1,4 - dihydro-4-oxoquinoline-3-carboxylic acid or 9-fluoro-8-(4-hydroxy-1-piperidinyl) - 5-methyl-6,7-dihydro-1-oxo-1H,5H-benzo[ij]quinolidine-2-carboxylic acid, or a  
5 pharmaceutically acceptable salt thereof.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 94/00266

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 5 A61K31/47

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US,A,4 399 134 (ISHIKAWA ET AL.) 16 August 1983 cited in the application ---	1,2
X	EP,A,0 287 951 (OTSUKA PHARM.) 26 October 1988 cited in the application see claim 1 ---	1,2
A	WO,A,91 07401 (SHERING CORP.) 30 May 1991 see page 3, line 19 - line 25 see pages 10,36,37 ---	3-6
A	US,A,4 894 374 (SKOTNICKI ET AL.) 16 January 1990 see column 1, line 5 - line 8 see claim 1 see column 4, line 50 - line 60 --- -/--	3-6

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
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- "P" document published prior to the international filing date but later than the priority date claimed

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- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
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Date of the actual completion of the international search

19 May 1994

Date of mailing of the international search report

30.05.94

Name and mailing address of the ISA

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Authorized officer

Gerli, P

# INTERNATIONAL SEARCH REPORT

Intern. al Application No  
PCT/JP 94/00266

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>DATABASE WPI Derwent Publications Ltd., London, GB; AN 84-173727 &amp; JP,A,59 095 220 (AJINOMOTO KK) 1 June 1984 see abstract -----</p>	3-6

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP 94/00266

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ **Claims Nos.:**  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claims 3-6 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ **Claims Nos.:**  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ **Claims Nos.:**  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 94/00266

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